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(54) **Sample observation apparatus and system, and method therefor particularly for biological samples.**

(57) A biological sample observation apparatus includes a solid-state image pickup element and a holding member. The holding member holds an observation target sample on an upper portion of a light-receiving portion of the solid-state image pickup element, at a predetermined distance therefrom, without an optical system. A biological sample observation system and method are also disclosed.

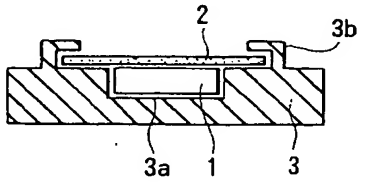

FIG.1

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Background of the Invention

The present invention relates to an apparatus and system for observing a sample, particularly biological sample, and a method therefor.

With the advent of a CCD (charge coupled device), solid-state image pickup elements have been developed greatly and the characteristics of the solid-state image pickup elements have considerably improved. Although a solid-state image pickup element is slightly inferior to a conventional camera tube in terms of resolution, it requires no optical system for forming an image. In addition, the function of photoelectric conversion of a large number of pixels, storage function, and charge read-out function of the solid-state image pickup element are integrated into an LSI as a solid-state image pickup device. Therefore, the solid-state image pickup element is superior to the camera tube in terms of ease in handling, prevention of sticking caused by intense light and of image distortion, and the like. Owing to such advantages, camera tubes have recently been replaced with solid-state image pickup elements in the field of broadcasting and the like.

Observation of minute biological samples such as cultured cells is mainly performed by a transmission type microscope. Especially for observation of a sample dipped in a liquid such as a culture medium, an inverted microscope having an objective lens arranged below the sample is used. When a microscopic image is recorded, a camera or a video camera mounted on the microscope is used. In addition, especially in observation of a cultured cell, if the temperature, humidity, and carbon dioxide concentration of the sample must be kept constant, a heat insulating unit, a humidifier, a carbonic acid gas supply unit, and the like are mounted on the sample table of the microscope.

An example of observation of a biological sample by means of a solid-state image pickup element is disclosed in Japanese Patent Laid-Open No. 2-208541. The disclosed apparatus is designed to detect an immunologic agglutination reaction. In the apparatus, a light-emitting diode is mounted on an agglutination reaction inspection plate, and a light-shielding mask, a condenser lens, and a one-dimensional CCD sensor are arranged below the plate in this order.

A microscope is an optical system including several lenses, prisms, mirrors, and the like. The size of this instrument including optical paths for forming images is considerably large. The size of the instrument is further increased if it includes a video camera required for recording images, and units for keeping the environment of a sample constant, e.g., a heat insulating unit, a humidifier, and a carbonic acid gas supply unit.

Furthermore, since a microscope is a high-precision instrument, it demands careful handling. Therefore, once, for example, the optical axis is shifted, special skills are needed in adjustment of the optical axis.

Moreover, in general, the heat insulating unit, the humidifier, the carbonic acid gas supply unit, and the like mounted on the sample table of the microscope easily cause variations in condition such as a variation in temperature as compared with an incubator for performing normal cell cultivation. Since it is difficult to reproduce the same environment as that of the incubator on the sample table, accurate observation is difficult to perform.

In a conventional biological sample observation apparatus using a solid-state image pickup element, since an optical system including several lenses is arranged between a sample and the image pickup element, problems similar to those in the microscope are posed, i.e., the size of the apparatus is increased, careful handling and adjustment for forming images are demanded, and the like.

Summary of the Invention

It is an object of the present invention to provide a biological sample observation apparatus and system, which have simple structures and can be easily operated, and a method therefor.

It is another object of the present invention to provide a sample observation apparatus and system, which can maintain a proper sample environment, and a method therefor.

It is still another object of the present invention to provide a sample observation apparatus and system, which allow continuous observation of an observation target sample while maintaining the environment of the target sample, and a method therefor.

These objects are particularly important for biological samples.

According to an aspect of the present invention, there is provided a sample observation apparatus comprising a solid-state image pickup element; and a holding member for holding an observation target sample adjacent a light-receiving portion of said image pickup element, at a predetermined distance therefrom, to permit observation of the sample by the image pickup element without an optical system.

According to another aspect of the present invention, there is provided a sample observation system comprising at least one sample observation apparatus as set forth above, driving means for driving the solid-state image pickup element arranged in the sample observation apparatus, and display means for performing data display of a sample image in accordance with an output signal from the solid-state image pickup element.

According to still another aspect of the present invention, there is provided a sample observation method comprising the steps of holding an observation target sample adjacent a light-receiving portion of a

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solid-state image pickup element without an optical system; and reading data from the target sample by driving said solid-state image pickup element, and obtaining a sample image by using an output signal from the image pickup element.

In each of the aforesaid aspects the sample may be a biological sample.

In each of the aforesaid aspects the holding member may be arranged to hold the sample on an upper portion of the light-receiving portion of the image pickup element.

Brief Description of the Drawings

Fig. 1 is a sectional view showing a biological sample observation apparatus according to an embodiment of the present invention;

Fig. 2 is a sectional view showing a biological sample observation apparatus according to another embodiment of the present invention;

Fig. 3 is a sectional view showing a biological sample observation apparatus according to still another embodiment of the present invention;

Fig. 4 is a block diagram showing a biological sample observation system according to an embodiment of the present invention; and

Fig. 5 is a biological sample observation system according to another embodiment of the present invention.

Description of the Preferred Embodiments

Embodiments of the present invention will be describe below with reference to the accompanying drawings.

Fig. 1 is a sectional view showing a biological sample observation apparatus according to an embodiment of the present invention. Referring to Fig. 1, reference numeral 1 denotes a solid-state image pickup element such as a CCD; 2, an observation target sample; and 3, a holding member having a recess portion 3a for containing the solid-state image pickup element 1 at an upper central position of the member, and holding arms 3b surrounding the recess portion 3a and designed to hold the sample 2. Each holding arm 3b has an inverted L-shaped cross-section. The sample 2 held by the holding member 3 has an observation target portion located immediately above the light-receiving surface of the solid-state image pickup element 1 at a predetermined distance therefrom. With this structure, the apparatus requires no optical system between the sample and the solid-state image pickup element, unlike a conventional apparatus. Therefore, the apparatus is greatly simplified.

The distance between the solid-state image pickup element 1 and the sample 2 is preferably set to be 1 cm or less in order to prevent an out-of-focus state of an image. Within this range, a transparent plate can be inserted between the solid-state image pickup element 1 and the sample 2 to protect the element 1, or a sharp image can be obtained by inserting a filter for limiting all incident light or light having a specific wavelength.

If the apparatus includes a mechanism for moving the holding member 3 with respect to the solid-state image pickup element 1, it can be suitably applied to observation of a sample larger than the light-receiving surface of the element 1. In addition, by changing the shape of the holding member 3, not only the plate-like sample shown in Fig. 1 but also a sample such as a petri dish containing a culture solution can be observed.

Since the apparatus includes no light source, it can be suitably applied to observation of a sample emitting light with a phosphor marker in a dark place. It is obvious that if only the light-receiving portion of the apparatus is covered to prevent external light from entering the apparatus, observation need not be performed in a darkroom.

Fig. 2 is a sectional view showing a biological sample observation apparatus according to another embodiment of the present invention. This apparatus is designed to receive external light to allow observation of a sample which emits no light. In addition to the components of the apparatus shown in Fig. 1, this apparatus includes a cap-like darkroom member 11 having a window 11a on a ceiling portion 11b and placed on the holding member 3 to cover the sample 2, and a filter 4 arranged at the window 11a located above the sample 2 and designed to reduce the amount of external light. Light adjusted by the filter 4 is guided to the light-receiving surface of a solid-state image pickup element 1.

It is preferable that rays of light having an intensity matching the characteristics of the solid-state image pickup element 1 and the same traveling direction be radiated on the light-receiving surface of the element 1. In order to satisfy such a condition, as the filter 4, one or a combination of the following components can be used: a filter, a diaphragm, a pinhole, a slit, and a deflection plate, which are designed to reduce the amount of external light or align rays in the same traveling direction, a scattering plate for scattering light, and a color filter for transmitting light having a specific wavelength.

Fig. 3 is a sectional view showing a biological sample observation apparatus according to still another embodiment of the present invention. In addition to the components of the apparatus shown in Fig. 2, this apparatus includes a roof portion 11c on a ceiling portion 11b of a darkroom member 11. A light source 5 is arranged on the roof portion 11c above a filter 4. For example, the intensity of light from the light source 5 is adjusted by the filter 4. The resultant light is then incident on the light-receiving surface of a solid-state image pickup element 1. Since the intensity of light

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can be easily controlled by changing an applied voltage or the like, a sharper image can be obtained as compared with the apparatus shown in Fig. 2. The apparatus may include a plurality of light sources. As light sources, light bulbs, light-emitting diodes, electroluminescence elements, and the like can be used.

Fig. 4 shows the arrangement of a biological sample observation system according to an embodiment of the present invention. As a biological sample observation apparatus 6, either an apparatus of the type having no light source, shown in Figs. 1 and 2, or an apparatus of the type having a light source, shown in Fig. 3, can be used. A solid-state image pickup element 1 in the biological sample observation apparatus 6 is driven by a driving section 7 to perform a reading operation. Image information from this element 1 is supplied to a display section 8 through the driving section 7. As a result, a sample image is data-displayed. If the display section 8 includes an image recording function and an image digital processing function as well as an image display function, a system suitable for a given purpose of observation can be realized.

In addition, a plurality of biological sample observation apparatuses 6 may be prepared to be selectively connected to the single driving section 7 and the single display section 8 by a switching control scheme. Alternatively, pairs of biological sample observation apparatuses 6 and driving sections 7 may be prepared to be selectively connected to the single display section 8 by a switching control scheme. With such a system, a large number of samples can be observed at once.

Fig. 5 shows the arrangement of a biological sample observation system according to another embodiment of the present invention. This system is characterized in that only the biological sample observation apparatus 6 in the system shown in Fig. 4 is housed in an incubator 9. The incubator 9 can control the internal temperature, humidity, and gas concentration, e.g., carbon dioxide concentration to keep them constant. Since a sample 2 is placed in the incubator together with the biological sample observation apparatus 6, observation of the biological sample can be performed in a well-controlled environment. This system is especially suitable for continuous observation of cells or bacteria.

If a light source 10 is arranged in the incubator 9 to control the amount of light, since the light source 5 need not be arranged in the biological sample observation apparatus 6, the apparatus can be simplified accordingly. This system is especially suitable for a case wherein a plurality of samples are observed by different biological sample observation apparatuses, because.the same observation conditions can be set for the respective apparatuses.

Examples of observation based on a biological sample observation method of the present invention will be described next.

Example 1: Analysis of an electromigration gel was performed on the basis of the biological sample observation method of the present invention. Electromigration of a sample was performed by using Phast Gel Gradient 10-15 available from Pharmacia Fine Chemicals, Inc. After a gel film was dyed, the film was placed on a biological sample observation apparatus of the present invention to observe an electromigration pattern. Digital image processing of the obtained image was performed by a personal computer to detect the position and density of a band, thereby identifying a protein in the sample.

This analysis method requires no laser, unlike a method using a densitometer, and hence allows a reduction in size of the apparatus. In addition, since scanning of laser light is not performed, the time required for measurement can be shortened.

Example 2: An immunologic agglutination reaction was detected on the basis of the biological sample observation method of the present invention. A transparent petri dish was placed on a biological sample observation apparatus of the present invention. The petri dish contained 2 mℓ of 9-mmol phosphate buffer (pH 7.4) containing 3.5 mg of latex (particle diameter: 1.08 μm; Sekisui Chemical Co., Ltd.) sensitized with hCG antibody (Medics Biochemica Inc.). The petri dish and the apparatus were placed in an incubator. After the sample containing hCG was added to the petri dish, observation of the petri dish was started. The hCG concentration in the sample was determined by observing the number of latex particles, which agglomerated due to an immunologic reaction and allowed to settle, over time.

Example 3: Observation of cultured cells was performed on the basis of the biological sample observation method of the present invention. 2 mℓ of an aqueous solution containing 0.03% of collagen and 0.2% of acetic acid was put in a polystyrene petri dish available from Falcon Inc, and the petri dish was left to stand for 10 min to adsorb the collagen. 1,000,000 rat hepotocytes together with a culture medium were placed on the petri dish which was washed with water. The petri dish was fixed in a biological sample observation apparatus of the present invention. The petri dish and the apparatus were placed in an incubator at a temperature of 37°C, a humidity of 90%, and a carbon dioxide concentration of 5%. Cultivation was continued for 18 hours, and changes in the cells were observed.

As has been described above, in each biological sample observation apparatus of the present invention, since an observation target sample is directly held on the upper portion of the light-receiving portion of a solid-state image pickup element, an optical system including lenses and the like, which is required in the prior art such as a microscope, can be omitted. Therefore, the size of the apparatus can be reduced. In addition, if light having a proper intensity can be en-

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sured, or a sample with a phosphor marker is used, no light source is required. This further simplifies the apparatus. Furthermore, since the apparatus has a simple structure and uses no fragile members such as vacuum tubes and lenses, it is resistant to careless handling, i.e., impact and the like. Since adjustment for forming an image, e.g., focusing, is not required, observation is facilitated.

If the apparatus includes a light source for radiating light on the light-receiving portion of an element through a sample, the intensity of light can be easily controlled by changing an applied voltage or the like, thus obtaining a sharper image.

In addition, the biological sample observation apparatus in which a sample is held on the upper portion of the solid-state image pickup element can be formed into a biological sample observation system suitable for a given purpose of observation by connecting a driving section for driving the element to a display section for displaying a sample image in accordance with an output signal from the element. Especially, if a plurality of biological sample observation apparatuses are prepared to be selectively connected to the driving section and the display section by a switching control scheme, a large number of samples can be observed at once. Furthermore, in this system, the size of the biological sample observation apparatus is small, and the apparatus is free from the problem of lens distortion at a high temperature, the problem of blurring of an optical system at a high humidity, and the like. Therefore, this apparatus can be used in combination with a control chamber in which the temperature, humidity, gas concentration, and the like are controlled. For example, the apparatus can be placed in an incubator for performing normal cell cultivation. That is, the use of the system of the present invention allows continuous observation of a biological sample under proper conditions of temperature, humidity, and gas concentration. The system is especially suitable for continuous observation of cells and bacteria.

Moreover, in this system, a light source is arranged in the control chamber to also control light radiated on a sample. With this arrangement, no light source need be arranged in the biological sample observation apparatus. If a plurality of apparatuses are arranged in the control chamber, the same observation conditions can be set for the respective apparatuses.

Claims

1. A sample observation apparatus characterized by comprising:

   a solid-state image pickup element (1); and

   a holding member (3) for holding an observation target sample (2) adjacent a light-receiving portion of said image pickup element (1), at a predetermined distance therefrom, to permit observation of the sample by the image pickup element (1) without an optical system.

2. A sample observation system characterized by comprising at least one apparatus according to Claim 1;

   driving means (7) for driving said solid-state image pickup element (1) arranged in said sample observation apparatus (6); and

   display means (8) for performing data display of a sample image in accordance with an output signal from said solid-state image pickup element (1).

3. A sample observation method characterized by comprising the steps of:

   holding an observation target sample adjacent a light-receiving portion of a solid-state image pickup element without an optical system; and

   reading data from the target sample by driving said solid-state image pickup element, and obtaining a sample image by using an output signal from the image pickup element.

4. A biological sample observation apparatus characterized by comprising:

   a solid-state image pickup element (1); and

   a holding member (3) for holding an observation target sample (2) on an upper portion of a light-receiving portion of said solid-state image pickup element (1), at a predetermined distance therefrom, without an optical system.

5. An apparatus according to claim 1 or Claim 4, wherein said holding member (3) comprises a recess portion (3a) for containing the observation target sample on an upper portion thereof, and holding arms (3b) having an inverted L-shaped cross-section, surrounding said recess portion (3a), and designed to hold the target sample.

6. An apparatus according to claim 1, 4 or 5 further comprising a cap-like darkroom portion (11) having a window (11a) on a ceiling portion (11b) and placed on said holding member (3) to cover the target sample, and a filter (4), fitted in the window (11a), for adjusting an amount of external light.

7. An apparatus according to any of Claims 1, 4, 5 or 6 further comprising a light source (5) for radiating light on the light-receiving portion of said solid-state image pickup element (1) through the target sample.

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8. A biological sample observation system characterized by comprising:

at least one biological sample observation apparatus (6) including a solid-state image pickup element (1), and a holding member (3) for holding an observation target sample on an upper portion of a light-receiving portion of said solid-state image pickup element (1), at a predetermined distance therefrom, without an optical system;

driving means (7) for driving said solid-state image pickup element (1) arranged in said biological sample observation apparatus (6); and

display means (8) for performing data display of a sample image in accordance with an output signal from said solid-state image pickup element (1).

9. A system according to claim 8, further comprising a control chamber (9) for housing said biological sample observation apparatus (6) and controlling an external environment thereof.

10. A system according to claim 8 or claim 9, further comprising a control chamber (9) for housing said biological sample observation apparatus (6) and controlling light to be radiated on the target sample.

11. A biological sample observation method characterized by comprising the steps of:

holding an observation target sample on an upper portion of a light-receiving portion of a solid-state image pickup element without an optical system; and

reading data from the target sample by driving said solid-state image pickup element, and obtaining a sample image by using an output signal from the target sample.

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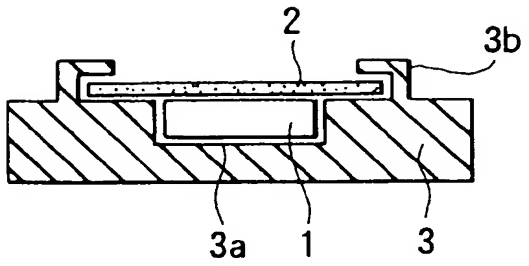

FIG.1

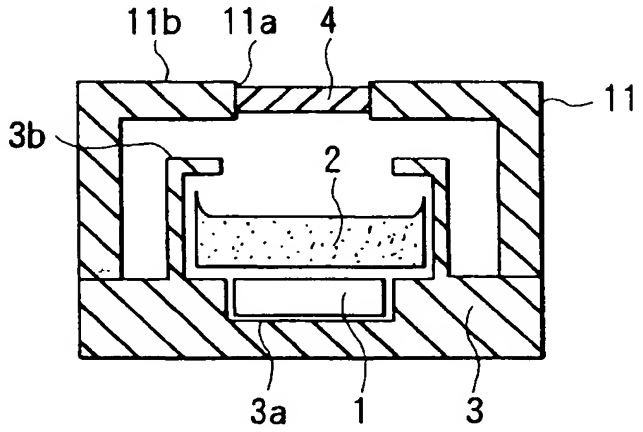

FIG.2

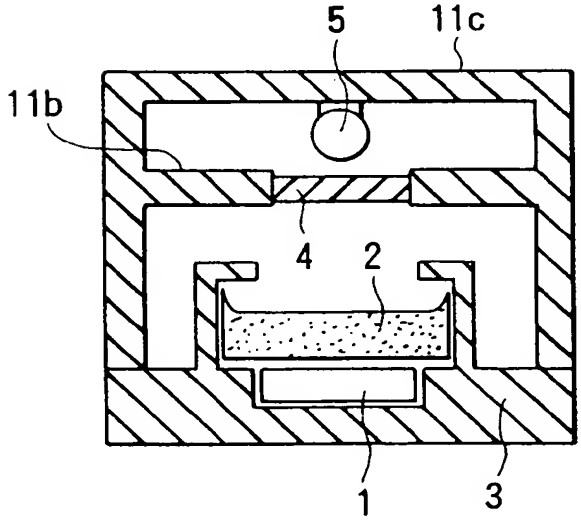

FIG.3

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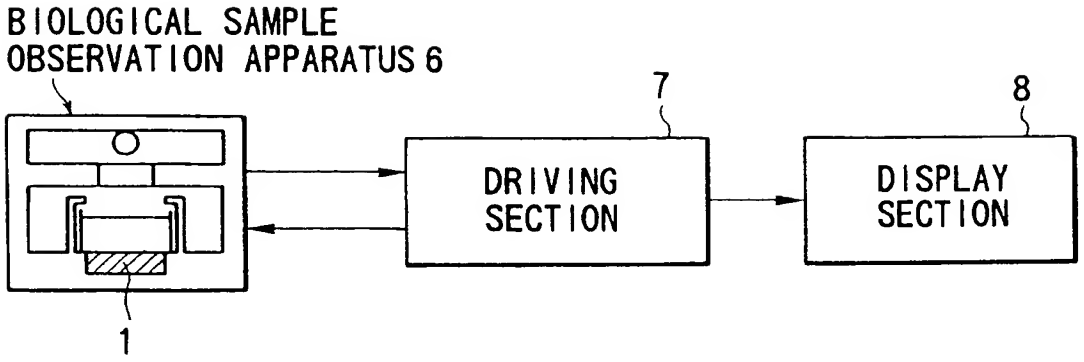

FIG.4

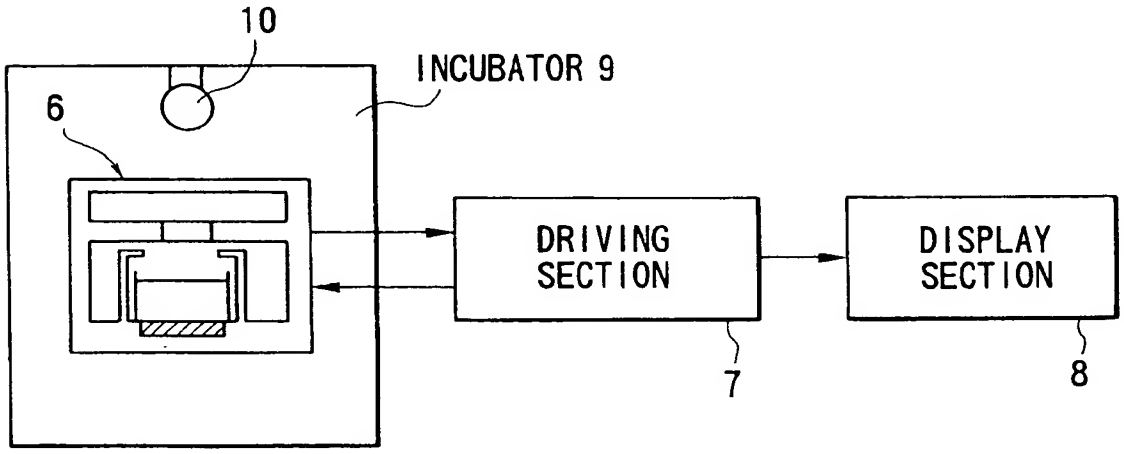

FIG.5

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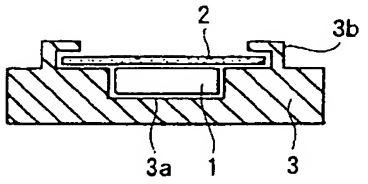

FIG.1

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 92 30 3257

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	WO-A-8 804 045 (J. RUSHBROOKE ET AL) * page 4, paragraph 3 - page 8, paragraph 3 ; page 14, paragraph 5 - page 15, paragraph 1; page 18, paragraph 2 - page 19, paragraph 2; page 24, paragraph 3; figures 1,8 *	1-5,8,11	G01N21/01 G01N21/76 G01N21/17
A	DE-A-3 812 899 (W. HEIL) * the whole document *	1-4,6-8, 11	
A	PATENT ABSTRACTS OF JAPAN vol. 13, no. 185 (P-865)2 May 1989 & JP-A-01 013 457 (SHINTO PAINT) 18 January 1989 * abstract *	1-4,7-11	
A	TRAC, TRENDS IN ANALYTICAL CHEMISTRY vol. 9, no. 8, September 1990, AMSTERDAM NL pages 269 - 277 C.E. HOOPER ET AL: 'Quantitative luminescence imaging in the biosciences using the CCD camera: analysis of macro and micro samples'		

TECHNICAL FIELDS SEARCHED (Int. Cl.5)
G01N C12M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	28 MAY 1993	JOHNSON K.

CATEGORY OF CITED DOCUMENTS

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